LIVER DISEASE IN YOUNG WOMEN WITH HYPERGLOBULINEMIA

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Several investigators have suggested that young women with a syndrome characterized by hyperglobulinemia, arthralgia or arthritis, febrile episodes and menstrual aberrations suffered from a peculiar or specific hepatic disorder. In a number of cases positive L.E. cell tests and acne, hirsutism, cutaneous striae and obesity were noted. In contrast to the usual patient with cirrhosis, these young women were frequently well nourished when first examined. Some observers have characterized the lesion as an "unusual form of cirrhosis"; others, stressing the occasional positive L.E. cell test, considered the disorder to be a manifestation or variant of disseminated lupus erythematosus. Accordingly the terms "lupoid hepatitis" or "hepatic lupus" have been proposed. The demonstration of circulating complement-fixing antibodies, with the use of liver antigen, and the observation of hepatic exudates rich in plasma cells have led to the concept that the disorder was of autoimmune nature.

In an attempt to determine whether the lesions were unique, constant in pattern or specific in etiology, we have carried out a microscopic investigation of the livers in 15 young women who presented many or all of the clinical features that have been considered indicative of this presumed entity (Table I). The potential role of immune mechanisms in the production of hepatic alteration has been considered in these cases and in the pertinent literature. The patients comprising this study group were selected on the basis of age, sex and clinical manifestations, without knowledge of the pathologic lesions. At the time of the apparent onset of the disease, the ages ranged from 10 to 21 years. All patients were observed at the Massachusetts General Hospital between 1942 and 1959. In 6 the pathologic examination was carried out on liver biopsy specimens procured during life. Necropsy tissue was used in the remaining 9 cases, in 2 of which liver biopsy had also been made ante mortem. The structural alterations analyzed included the intensity,
| Case no. | Age at onset (yr.) | Duration (death or recovery) (yr.) | Serum globulin (gm./100 ml.) | Arthralgia | Febrile episodes | Menses | Acne | Striae | "L.E."
<table>
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<tr>
<td>1</td>
<td>21</td>
<td>3/6 R (8 wk.)</td>
<td>3.8 - 6.7 (4.0 (+5 d.)</td>
<td>+</td>
<td>+</td>
<td>A</td>
<td>+</td>
<td>+</td>
<td>&quot;Probable&quot;</td>
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<tr>
<td>2</td>
<td>16</td>
<td>6 D</td>
<td>3.3 - 6.9 (3.4 (--20 d.)</td>
<td>o</td>
<td>+</td>
<td>A</td>
<td>+</td>
<td>+</td>
<td>n.d.</td>
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<tr>
<td>3</td>
<td>16</td>
<td>6 D</td>
<td>7.5 - 8.5 (7.5 (--1 d.)</td>
<td>o</td>
<td>+</td>
<td>A</td>
<td>+</td>
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<td>n.d.</td>
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<td>4</td>
<td>19</td>
<td>3 1/2 D</td>
<td>6.8 -11.2 (6.8 (--6 d.)</td>
<td>+</td>
<td>+</td>
<td>A</td>
<td>+</td>
<td>o</td>
<td>n.d.</td>
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<tr>
<td>5</td>
<td>16</td>
<td>3 D</td>
<td>3.5 - 5.6 (5.6 (+4 d.)</td>
<td>o</td>
<td>+</td>
<td>A</td>
<td>+</td>
<td>o</td>
<td>n.d.</td>
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<td>6</td>
<td>16</td>
<td>7 D</td>
<td>4.5 - 5.7 (5.0 (--4 d.)</td>
<td>+</td>
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<td>A</td>
<td>+</td>
<td>+</td>
<td>n.d.</td>
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<tr>
<td>7</td>
<td>13</td>
<td>7 D</td>
<td>2.8 - 5.7 (3.4 (--1 d.)</td>
<td>+</td>
<td>+</td>
<td>A</td>
<td>+</td>
<td>+</td>
<td>n.d.</td>
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<tr>
<td>8</td>
<td>10</td>
<td>7 D</td>
<td>3.1 - 5.1 (4.6 (--2 d.)</td>
<td>o</td>
<td>+</td>
<td>A</td>
<td>+</td>
<td>+</td>
<td>n.d.</td>
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<tr>
<td>9</td>
<td>11</td>
<td>6 D</td>
<td>2.8 - 5.3 (2.8 (--370 d.)</td>
<td>o</td>
<td>o</td>
<td>A</td>
<td>+</td>
<td>+</td>
<td>n.d.</td>
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<tr>
<td>10</td>
<td>20</td>
<td>3 D</td>
<td>1.8 - 3.7 (3.7 (--2 d.)</td>
<td>o</td>
<td>N</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>n.d.</td>
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<tr>
<td>11</td>
<td>10</td>
<td>4 1/2 D</td>
<td>3.5 - 6.2 (3.6 (--8 d.)</td>
<td>o</td>
<td>o</td>
<td>+</td>
<td>+</td>
<td>o</td>
<td>n.d.</td>
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<tr>
<td>12</td>
<td>13</td>
<td>3/4 D</td>
<td>3.1 - 4.8 (3.8 (--90 d.)</td>
<td>+</td>
<td>+</td>
<td>A</td>
<td>+</td>
<td>+</td>
<td>n.d.</td>
</tr>
<tr>
<td>13</td>
<td>14</td>
<td>8 L</td>
<td>5.0 - 7.6 (7.1 (+8 d.)</td>
<td>+</td>
<td>+</td>
<td>A</td>
<td>+</td>
<td>o</td>
<td>n.d.</td>
</tr>
<tr>
<td>14</td>
<td>16</td>
<td>3 D</td>
<td>3.9 - 8.2 (3.9 (--2 d.)</td>
<td>o</td>
<td>+</td>
<td>A</td>
<td>o</td>
<td>o</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>14</td>
<td>6 D</td>
<td>3.3 - 6.0 (4.0 (--14 d.)</td>
<td>+</td>
<td>+</td>
<td>A</td>
<td>+</td>
<td>o</td>
<td>n.d.</td>
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</table>

* The interval between examination of histologic specimen and the nearest serum globulin value is indicated in brackets as days (d.) before (−) or after (+).

A = Amenorrhea.
N = Normal menses.
† History inadequate to evaluate menses.
D = Died.
R = Living with marked clinical improvement.
L = Living with continuing evidence of liver disease.
nature and location of the inflammatory response, the pattern of fibrosis, when present, and parenchymal features such as cell necrosis and regenerative activity.

To determine whether the lesions encountered were of specific nature, the tissue sections were compared with those from 6 control groups made up of men and women whose ages ranged from 16 to 75 years. In none of these were the clinical features peculiar to the study group evidenced. The control groups were (a) postnecrotic cirrhosis, 27 cases (15 necropsy and 12 biopsy specimens); (b) posthepatitic cirrhosis, 23 cases (15 necropsy and 8 biopsy specimens); (c) fatal viral hepatitis, 10 cases (all necropsy specimens); (d) nonfatal viral hepatitis, 15 cases (all needle biopsy specimens); (e) disseminated lupus erythematosus, 18 cases (all necropsy specimens); (f) chronic, nonspecific hepatitis, 15 cases (all needle biopsy specimens).

The examples of postnecrotic and posthepatitic cirrhosis fulfilled the pathologic criteria outlined by Gall; fatal and nonfatal hepatitis have also been authoritatively documented. The sections of chronic nonspecific hepatitis resembled those described by Schaffner and Popper and, as the name implies, were characterized by minimal hepatic structural abnormality and an association with a variety of extra-hepatic diseases.

RESULTS

Five different structural patterns were found in the study group (Table II); there was, however, uniformity of pattern in all liver sections in a given case. In one patient (case 1) the lesion proved to be that

| Table II |
| INCIDENCE OF HEPATIC LESIONS |

<table>
<thead>
<tr>
<th>Anatomic diagnosis</th>
<th>No. of cases</th>
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<tbody>
<tr>
<td>Infectious hepatitis</td>
<td>1</td>
</tr>
<tr>
<td>Subacute hepatic necrosis</td>
<td>5</td>
</tr>
<tr>
<td>Posthepatitic cirrhosis with chronic hepatitis</td>
<td>3</td>
</tr>
<tr>
<td>Postnecrotic cirrhosis with chronic hepatitis</td>
<td>5</td>
</tr>
<tr>
<td>Posthepatitic cirrhosis</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15</strong></td>
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</table>

of severe, nonfatal, acute viral hepatitis, exhibiting universal portal area exudation, lobular disarray, and parenchymal infiltration by lymphocytes. There were, in addition, "balloon" cells, eosinophilic hyaline bodies, prominence of Kupffer cells, and evidence of parenchymal regeneration (Figs. 1 and 2). The onset of this patient’s illness suggested infectious hepatitis, and there was progressive clinical improvement over
the subsequent 8 weeks before discharge from the hospital. In several of the control cases of hepatitis (group d) the lesions were indistinguishable from the process in this case.

In 5 instances (cases 2 to 6) subacute hepatic necrosis was found. There were submassive necrosis, stromal collapse, proliferating “pseudoductules,” and extensive stromal infiltration by lymphocytes and plasma cells (Figs. 3 and 4). In general, the reticulin framework was intact, and there was little or no formation of collagen. In 2 instances (cases 2 and 4) the typical lesions of acute viral hepatitis had been revealed by biopsy 6 and 3½ years previously. In 1 case (case 6) the clinical history suggested anicteric hepatitis preceding the onset of clinically overt liver disease. All the patients in this group died in hepatic failure between 3 and 6 years after the apparent onset. In 2 of the 10 control cases of fatal hepatitis (group c), 4 and 6 weeks’ duration, alterations were identical to those in the 5 study patients.

The most common pattern, that of cirrhosis accompanied by marked chronic inflammation, was seen in 8 specimens (cases 7 to 14). These were characterized as cirrhosis with chronic hepatitis to indicate the exuberant chronic inflammation and focal hepatic cell necrosis accompanying the band fibrosis and nodular regeneration. The inflammatory response was most severe in the stroma adjacent to the parenchyma, and necrosis was evident at the periphery of regenerated nodules and surviving lobules. This pattern of necrosis has been designated “peripheral piecemeal necrosis” by Popper. Posthepatitic cirrhosis was present in 3 of the cases (cases 7 to 9) (Figs. 5 and 6), and postnecrotic cirrhosis appeared in 5 (cases 10 to 14) (Figs. 7 and 8). One patient (case 11) had apparently had anicteric hepatitis, and all but one (case 13) died in hepatic failure; the duration of the illness ranged from 9 months to 7 years. A comparable degree of chronic inflammation and cell necrosis was found in only 2 of the 50 cases of posthepatitic and postnecrotic cirrhosis among the controls (groups a and b); both were middle-aged men who were undergoing portal vein shunt procedures.

In one instance (case 15) inactive posthepatitic cirrhosis was manifest (Fig. 9). The lesion here had features similar to those in control examples of posthepatitic cirrhosis. Narrow, well-collagenized fibrous bands joined portal areas, and centrilobular veins were intact. Inflammation was minimal and cellular necrosis was virtually absent, features in sharp contrast to the exudate and necrosis found in all the other cases. This patient had had anicteric hepatitis shortly after her father had suffered an attack of infectious hepatitis; she died in liver failure 6 years after the onset.

In view of the emphasis placed on plasma cell infiltration in previous
reports, we compared its intensity in the study group with the appropriate controls and found that in only 5 of the 15 study cases (cases 2 to 4, 12 and 13) was the exudate more abundant than in the control specimens.

None of the 15 women in the study group had lesions resembling those found in patients with disseminated lupus erythematosus or nonspecific hepatitis (groups e and f). In the 9 patients examined at necropsy, nothing indicative of lupus erythematosus was found; lacking were hematoxylin bodies, splenic periarterial fibrosis, and thickening of the glomerular basement membranes. Among the 18 patients who died of lupus erythematosus (group f), the liver was normal in 13, and in the remaining 5 only minimal focal, fatty changes were present.

Most of the patients had illnesses of long duration (Table III). Three years was the mean duration among patients with both subacute hepatic necrosis and those with cirrhosis and chronic hepatitis. Although one

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Anatomic diagnosis</th>
<th>Interval (yr.)</th>
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<tbody>
<tr>
<td>1</td>
<td>Infectious hepatitis</td>
<td>1/2</td>
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<tr>
<td>2</td>
<td>Subacute hepatic necrosis</td>
<td>5</td>
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<tr>
<td>3</td>
<td>Subacute hepatic necrosis</td>
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<td>4</td>
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<td>5</td>
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<tr>
<td>6</td>
<td>Subacute hepatic necrosis</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>Posthepatitic cirrhosis with chronic hepatitis</td>
<td>5 1/2</td>
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<td>8</td>
<td>Posthepatitic cirrhosis with chronic hepatitis</td>
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<td>9</td>
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<tr>
<td>10</td>
<td>Postnecrotic cirrhosis with chronic hepatitis</td>
<td>2</td>
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<tr>
<td>11</td>
<td>Postnecrotic cirrhosis with chronic hepatitis</td>
<td>4 1/2</td>
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<tr>
<td>12</td>
<td>Postnecrotic cirrhosis with chronic hepatitis</td>
<td>9 1/2</td>
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<td>13</td>
<td>Postnecrotic cirrhosis with chronic hepatitis</td>
<td>1/2</td>
</tr>
<tr>
<td>14</td>
<td>Postnecrotic cirrhosis with chronic hepatitis</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>Posthepatitic cirrhosis</td>
<td>6</td>
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might expect the duration in cases of cirrhosis to be longer than in subacute hepatic necrosis, clinically inapparent disease preceding overt illness precludes accurate dating of the onset. In the two patients (cases 7 and 8) in whom both biopsy and necropsy material was available, the pattern was unchanged after 1 1/2 years and 9 months, respectively.

**Discussion**

This investigation was designed to determine the presence or absence of structural uniformity or specificity in the hepatic lesions in 15 young women with the curious clinical features noted above. Anatomic homogeneity proved not to be present, and the lesions were not unique in
nature. The incidence of hepatic necrosis and significant inflammation in excess of that encountered in the controls probably relates to the method of selection. A feature in the study group was elevation of serum globulin; it has been pointed out that moderate to marked serum globulin elevation in liver disease is usually associated with significant amounts of hepatic necrosis and chronic inflammation. In the sole example with minimal chronic inflammation (case 15), the serum globulin was elevated (4 gm.) 2 weeks prior to necropsy but had fallen from a high level of 6 gm. All patients had elevation of serum globulin near the time of pathologic examination except case 9, where the interval was 1 year.

The nature of the hepatic lesions varied among the 15 patients. In case 1, alterations were those of acute viral hepatitis. In 5 patients subacute hepatic necrosis was encountered. This lesion is nonspecific although in 2 of the patients (cases 2 and 4) a liver biopsy obtained early in their illnesses disclosed acute viral hepatitis. In another patient (case 6) a history indicating anicteric hepatitis was obtained. All 5 cases exhibited the structural features of fatal hepatitis with a subacute course described by Lucké and Klatskin. The latter author reported 9 cases of subacute hepatic necrosis developing after anicteric viral hepatitis. The anatomic lesions also corresponded to those described by Jersild, Salvesen and Lödöen, and Bjørneboe and Raaschou in cases of fatal viral hepatitis during Scandinavian epidemics. In the remaining 10 patients postnecrotic and posthepatitic cirrhosis was found. Postnecrotic cirrhosis may result from a variety of disorders including viral hepatitis. Posthepatitic cirrhosis is regarded as a sequela of a smoldering inflammation. Gall has stated, "Whether this is necessarily of infectious (viral) nature is not entirely clear."

An infectious viral background seems rather firmly established in 3 of the 15 patients (cases 1, 2 and 4). In each of these a diagnosis of acute infectious hepatitis was established by biopsy at some point in their illnesses. A similar basis was strongly suggested by history in 2 other patients (cases 6 and 15). The pathologic and clinical data in the remaining 10 cases do not permit the assumption of a specific cause. On the other hand, the hepatic alterations in these cases are similar to those which have been described following epidemic and sporadic hepatitis. These have been of varying duration and were very likely attributable to viral infection. It is worthy of note that none of the 15 women in the study group showed clinical evidence of alcoholism, malnutrition, or exposure to hepatotoxic substances, and anicteric hepatitis is said to occur more commonly in women than in men.

On the basis of various anatomic and immunologic observations, it has been suggested that immune mechanisms are partially or wholly re-
spouse for the hepatic lesions encountered in individuals with the syndrome serving as the basis for this report.\textsuperscript{9} The anatomic evidence rests primarily on the observation of exudates rich in plasma cells in the liver. In two thirds of our cases, however, the intensity of the plasma cell reaction was similar to that observed in comparable control groups. The demonstration of complement-fixing antibodies, interpreted as auto-antibodies, comprises the principal immunologic indication that the hepatic lesion might result from an autoimmune mechanism.\textsuperscript{9} It should be pointed out, however, that complement-fixing antibodies have been demonstrated with liver and kidney antigens in a variety of diseases, including acute viral hepatitis, multiple myeloma, chronic biliary cirrhosis and disseminated lupus erythematosus.\textsuperscript{36} Furthermore, Hackett and Beech,\textsuperscript{37} using liver, kidney, adrenal, thyroid and lung antigens, have reported the demonstration of complement-fixing antibodies in 1 of 7 healthy student nurses undergoing prophylactic immunization; another member of the group also reacted, but only with kidney antigen. According to some, hyperglobulinemia may be indicative of excessive antibody production. However, a recent report\textsuperscript{38} of two patients with agammaglobulinemia, one dying with acute yellow atrophy and the other with postnecrotic cirrhosis following viral hepatitis, casts doubt on the premise that an autoimmune mechanism related to circulating antibodies is the cause of these lesions.

To date the arguments favoring immune or autoimmune mechanisms have not received strong support in the experimental induction of hepatic lesions. This is in contrast to other experimentally induced autoimmune conditions, such as thyroiditis.\textsuperscript{39} One group of investigators\textsuperscript{40} reported liver necrosis following the injection of homologous whole liver with adjuvant, but 80 per cent of the lesions developed within 72 to 96 hours after the injection. The rapidity of onset and the appearance of the lesions in illustrations published suggests that other factors than immune mechanisms were responsible. Attempts to reproduce these results have been unsuccessful,\textsuperscript{41} and it has also been demonstrated\textsuperscript{42} that adjuvant alone may produce hepatic injury. The fact that liver lesions have been induced by adrenal homogenates\textsuperscript{43} would make it doubtful that the changes effected by liver homogenates were of specific nature. The data currently available seem insufficient to prove or disprove the significance of autoimmunity as a basis for the initiation or perpetuation of hepatic disorders.

We have found no evidence that the hepatic lesions in our cases were related to disseminated lupus erythematosus. In none of the 9 patients examined at necropsy were lesions suggesting lupus found in other organs. Furthermore, examination of the liver sections from the 18 con-
trol cases of disseminated lupus erythematosus (group e) confirmed the findings of others \(^{44}\) that hepatic parenchymal changes were infrequent in this condition. Our experience has shown that abnormality of liver parenchyma in lupus rarely exceeds focal fatty degeneration. The proposal that the hepatic lesions in young women with hyperglobulinemia constitute a manifestation or variant of lupus erythematosus is based largely on the demonstration of L.E. cells in some of the cases. On the other hand, the tests are often described as weakly or transiently positive, and some observers \(^{5}\) have reported that when anticoagulants were used in performing the tests, the results were negative. In the one instance in our group (case 14) in which a positive L.E. cell test was observed, it was only a transient finding, and there were no other manifestations of lupus.

Our evaluation has shown that the hepatic lesions in the study group were not peculiar to these cases; they were found with varying frequency and intensity in comparable controls. There seems little justification for regarding the disorder in these young women as a specific entity on the basis of clinical features since many of the same phenomena, including arthralgia and hyperglobulinemia, have been encountered in children, \(^{31}\) post-menopausal women, \(^{45}\) and in men \(^{2}\) with liver disease.

**Summary**

The proposal that a form of liver disease exists among young persons, principally females, variously designated as “lupoid hepatitis” or “hepatic lupus,” stimulated a study of 15 young women exhibiting the allegedly specific clinical features.

Among these patients 5 different structural patterns were found: acute infectious hepatitis (1 case); subacute hepatic necrosis (5 cases); posthepatitic cirrhosis with chronic hepatitis (3 cases); postnecrotic cirrhosis with chronic hepatitis (5 cases); and inactive posthepatitic cirrhosis (1 case). The qualifying term “chronic hepatitis” was applied in 8 of the 9 instances of cirrhosis to indicate the presence of an abundant chronic inflammatory exudate, and focal parenchymal necrosis. These were in addition to the cirrhotic fibrosis and nodular regeneration.

The structural changes were not peculiar to these patients; identical lesions were adequately demonstrated in a large series of comparable controls.

In 5 of the cases an infectious viral cause was suggested by the appearance of the lesions of acute viral hepatitis in biopsy at some time during the course in 3 cases and a history indicative of anicteric hepatitis in 2 others. In the remaining 10 cases the etiology of the hepatic lesions could not be determined. Evidence of a relationship to lupus erythematosus was lacking.
REFERENCES


20. POPPER, H. Personal communication.


41. Tisdale, A. Unpublished data.


[Illustrations follow]
LEGENDS FOR FIGURES

Photomicrographs were prepared from sections stained with hematoxylin and eosin.

FIG. 1. Infectious hepatitis (case 1). Lobular disarray is accompanied by lymphocytic infiltration of the parenchyma. Foci of necrosis are distributed irregularly. × 37.

FIG. 2. Infectious hepatitis (case 1). Some hepatic cells have undergone extreme hydropic degeneration; occasional regenerating multinucleated cells are evident. × 140.

FIG. 3. Subacute hepatic necrosis (case 4). Lobular remnants appear as small islands of hepatic cells. There is edema, stromal collapse, but no collagen formation. × 38.

FIG. 4. Subacute hepatic necrosis (case 4). Irregular clusters of regenerating liver cells are accompanied by an inflammatory exudate composed of lymphocytes and plasma cells. × 200.
FIG. 5. Posthepatitic cirrhosis with chronic hepatitis (case 7). Thin fibrous septums encompass several lobules, leaving central veins intact. Lymphocytes and plasma cells align themselves at the periphery of residual lobules. × 38.

FIG. 6. Posthepatitic cirrhosis with chronic hepatitis (case 7). Regenerating, multinucleated hepatic cells border the periphery of a lobule. Intense exudation of lymphocytes appears in the adjacent fibrous stroma. × 200.

FIG. 7. Postnecrotic cirrhosis with chronic hepatitis (case 11). Irregular nodules of hepatic cells are embedded in a well-collagenized fibrous matrix. Lymphocytes and plasma cells infiltrate the broad fibrous bands. × 38.

FIG. 8. Postnecrotic cirrhosis with chronic hepatitis (case 11). Dense collections of lymphocytes and plasma cells penetrate into the periphery of a regenerated nodule, producing an irregular, ragged margin. × 200.

FIG. 9. Inactive posthepatitic cirrhosis (case 15). Narrow fibrous trabeculae course through the liver, encompassing several lobules. Inflammation is minimal. There is moderate post-mortem autolysis. × 38.